REMARKS

1. Rejection of claims 1-6 and claims 22-36 dependent thereon: In the final Office Action mailed July 6, 2009, the Examiner continues to reject claims 1-6 and 22-36 under 35 USC §103 (a) as being obvious over Tamura et al. (EP 1 082 963) in combination with Smith et al. (Arthritis & Rheumatism, 1999). The Applicant respectfully disagrees with the Examiner's analysis of the cited documents, and this final rejection is respectfully traversed.

The Examiner asserts that *"it would have been obvious to one having ordinary skill in the art...to modify the conjugate product of Tamura by the use of rhein, or a derivative thereof such as diacerein, as the therapeutic agent to be conjugated to HA and administer it for the treatment of osteoarthritis with a reasonable expectation of success because this agent is known to be used for this therapeutic method."* The Applicant strongly contests this assertion by the Examiner for the reasons that follow:

(i) First, contrary to the Examiner's assertion, Tamura fails to provide motivation to a person having ordinary skill in the art to prepare a conjugate of HA with <u>any</u> therapeutic agent that has an activity in joint diseases, <u>with a reasonable expectation of success</u>. Tamura describes and exemplifies conjugates of HA with a specific group of compounds, namely hydroxamic acid residues, which have a particular chemical structure. According to the findings of Tamura, the conjugates of HA with certain with certain exemplified hydroxamic residues exhibit the effects of remaining in the joint cavity for a long period of time, i.e., maintaining this activity of HA formulation, and do not affect the MMP inhibiting activity of the hydroxamic acid residue.

In view of the very different chemical structures and modes of action of the very large number of potential therapeutic agents having activity in joint diseases, the ordinarily skilled

person would be faced with an enormous burden of trying to form a conjugate of hyaluronic acid with every single compound known to have some activity in joint diseases just to test if indeed that they are able to form a conjugate that maintains the action of hyaluronic acid, e.g., retaining the conjugate at the joint site, and does not adversely affect the therapeutic effect of the agent for joint diseases. This task is made even more colossal when one considers that for each therapeutic agent there would be a number of different possible ways of trying to form the linkage with hyaluronic acid for forming the conjugate.

Moreover, in view of the very different structures and modes of actions of the very many different potential therapeutic agents for joint diseases, and considering how the pharmacological activity of compounds may vary greatly upon small changes in structure, stereochemistry, etc., the person of ordinary skill in the art would not be able to reasonably expect, from the results of the specific compounds taught in Tamura (i.e., the specific conjugates of HA with specific hydroxamic acid residues exemplified in Tamura), that a conjugate formed between hyaluronic acid and every single possible therapeutic agent having activity for joint disease would have the effects of the HA-hydroxamic acid conjugates exemplified by Tamura, i.e., of maintaining the activity of hyaluronic acid for retention of the compound in the joint, and not adversely affecting the activity of the therapeutic agent.

(ii) Second, it is emphasized that the compounds of the present invention, as claimed in claims 1-6, present important and unexpected advantages. Particularly, the compounds according to the present invention have the important advantage of exhibiting an improved activity for the inhibition of IL-1 induced MMP expression compared to the therapeutic agent rhein (see Example 7 and Figure 5 of the present application). Moreover, the compounds of the present

invention show an unexpectedly significantly improved long term shelf stability as compared to HA formulations, e.g., of a least 36 months at 4°C ± 0.5°C in aqueous solution.

The improved pharmacological activity of the compounds of the present invention compared to the therapeutic agent rhein is an unexpected and very advantageous technical effect.

At page 4 paragraph 2 of the final Office Action, the Examiner considers that Tamura teaches the conjugates described therein to exhibit a synergistic effect. It is respectfully requested that the passage of Tamura paragraph [0019] of Tamura cited by the Examiner be considered in its correct context. Indeed, it is only correct to consider also the first part of the sentence of Tamura's paragraph [0019] referred to by the Examiner, where it is stated, *"...similar to HA formulations, the conjugate of a therapeutic agent for joint diseases and HA, a derivative or a salt thereof, remained in a joint cavity for a long period of time after being administered into the joint cavity, thereby reducing systemic side effects accompanying the MMP inhibitor and maintaining the medical effect of HA and the therapeutic agent for joint diseases; ...."*

The "medical effect" of HA is explained in paragraph [0011] of Tamura, where it is explained that *"as a lubricant and also by enhancing HA production in the joints and the like, HA formulations ease the disorder of joint functions, although they do not inhibit MMPs...HA is characteristically localized within the joint cavity for a long time period after it is being injected....."*

It is stressed in Tamura many times, i.e., see paragraphs [0030], [0056], [0072], that it is an important feature of Tamura that the binding of therapeutic agent for joint diseases to the HA does not affect the activity of the therapeutic agent.

Accordingly, in view of the above, and further considering the conclusions of paragraphs [0147] to [0149] of Tamura, it is clear that the "synergism" referred to by Tamura is the effect of

providing that the conjugate compound exhibits the activity attributed to HA formulations of being retained for long periods of time at the joint, maintaining the activities of HA for easing joint function disorders and maintaining the MMP inhibition activity of the hydroxamic acid residue.

Nowhere in Tamura is it described, or even suggested, that a conjugate of HA and a therapeutic agent for joint diseases taught therein might have an improved activity for MMP inhibition compared to the therapeutic agent (MMP-inhibitor compound).

It is respectfully submitted that contrary to the conjugates taught by Tamura, the compounds of the present invention, as claimed, provide the unexpected advantage of exhibiting increased activity for inhibition of IL-1 induced MMP expression. It is respectfully submitted that the ordinarily skilled person in the art would not have any reasonable expectations that a compound according to the present invention, as claimed, would provide the observed improved pharmacological activity compared to the therapeutic agent rhein, based on the teachings of Tamura and Smith et al.

Further, it is also submitted that the only consideration given in Tamura to the stability of the conjugates described therein is a consideration of certain of the specific exemplified conjugates with respect to the stability of the bond joining the therapeutic agent and the hyaluronic acid moieties over a short period of time, whereby it was observed, see Figure 4 and Example 4, that the "conjugate No. 5" showed stability in the bond between HA and the hydroxiymic acid residue over a period of 5 days. It is respectfully submitted that on the basis of these results described in Tamura, the ordinarily skilled person would have no reason to expect that a conjugate of HA with rhein, or a derivative thereof, according to the present invention might provide the observed significant improvement of the long-term stability of HA as

compared to known hyaluronic acid formulations, particularly respect to hydrolytic degradation, (e.g., compounds of the present invention showed stability of a least 36 months at 4°C ± 0.5°C in aqueous solution).

Accordingly, in view of the above, it is respectfully submitted that the compounds of the present invention as claimed in claims 1-6, and all claims dependent thereon, are non-obvious over the combination of the cited documents Tamura and Smith et al.

2. Rejection of claims 1-11 and claims 22-36 dependent thereon: Concerning the Examiner's rejection of the claims 1-11 and 22-36 as being obvious under 35 U.S.C. §103 (a) over the combination of Tamura et al. and Smith and et al., in view of Nguyen et al. (US 5,612,321), the claim rejections based on this combination of prior art documents are respectfully traversed.

Nguyen is cited by the Examiner "merely" with respect to "teaching a synthetic method," and the Examiner acknowledges that Nguyen has no relevance with respect to the compounds of claims 1-6. Accordingly, it is understood that the Examiner's rejection relates specifically to the claims 7-11.

Since the compound necessarily produced by the process of claim 7 (i.e., by the reaction of acid chloride of rhein, as such or in derived form, with hyaluronic acid) is a compound according to claims 1-6, which compounds have clearly been shown to be non-obvious over the combination of Tamura and Smith et al., as discussed in detail above, then a process according to claim 7 is inherently non-obvious over the cited prior art, and therefore the Examiner's rejections with respect to claim 7, and claims 8-11 dependent thereon, are moot.

In addition to the arguments presented above showing clearly the non-obviousness of the compounds of the present invention over the combination of Tamura and Smith et al., it is further

submitted that Nguyen teaches a process for the preparation of certain anti-oxidant grafted polysaccharides (by reaction of the polysaccharide with a hydroxyl-reactive anti-oxidant derivative) that involves a number of steps.

In a first step, an HA sodium salt must be converted to a tetra-alkyl ammonium salt, and then the tetra-alkyl ammonium salt of HA is reacted with an acid chloride, and then in a further step the produced compound is subjected to an ion-exchange reaction to convert the product to the sodium salt of the grafted compound.

Accordingly, Nguyen does not teach the method of claim 7 in which HA is itself reacted with an acid chloride in a single step to form the product HA-rhein ester compound, thereby avoiding the disadvantages of the additional steps required by the method taught by Nguyen. Accordingly, this provides yet a further reason why the process of claim 7 and the claims dependent thereon is clearly non-obvious over the combination of the cited documents, Tamura, Smith et al. and Nguyen et al.

3. Rejection of claims 1-15 and claims 22-32 dependent thereon: Concerning the Examiner's rejection of claims 1-15 and 22-32 as being obvious under 35 U.S.C. §103 (a) over Tamura et al. and Smith et al. in view of Nguyen et al. and Hubbell et al. (US 5,834,274), it is understood from the Examiner's arguments that this rejection is specifically relating to the process claims 12-15.

It has already been shown above that the claims to the compound, claims 1-6, and claims 7-11 to the process for the preparation of the compounds of claims 1-6, and the remaining claims 22-36 dependent on the product claims 1-6, are all non-obvious under 35 U.S.C. §103 (a). Since the claims 12-15 rejected in this section of the Office Action are dependent upon claim 7, these claims are thereby inherently non-obvious, as well, and the Examiner's rejections are moot.

4. Rejection of claims 1-11 and claims 16-36 dependent thereon: With respect to the Examiner's rejection of claims 1-11 and 16-36 on the ground of obviousness under 35 U.S.C. §103 (a) over Tamura et al. and Smith et al. in view of Nguyen et al. and Kuhla et al. (US 4,788,187), it is understood that this rejection refers specifically to claims 16-21.

It has already been mentioned above that the compounds of the present invention as claimed in the claims 1-6 are non-obvious over the cited prior art. The independent process claim 7, which necessarily results in the preparation of a compound according to claims 1-6, is inherently non-obvious, and has been shown to be non-obvious over the specific combinations of prior art documents cited by the Examiner. Accordingly, claims 16-21, which are dependent on claim 7, are accordingly non-obvious, as well, over the cited prior art. The Examiner's rejections with respect to claims 1-11 and 16-32 are thereby moot.

Accordingly, it is respectfully submitted, that all pending claims 1-36 are patentable over all the cited prior art documents.

Respectfully submitted,

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